REMARKS

The title has been deleted and a new title which more accurately reflects the instant invention has been submitted.

The previously submitted "CROSS-REFERENCE TO RELATED APPLICATIONS" paragraph has been replaced with a new "CROSS-REFERENCE TO RELATED APPLICATIONS" paragraph in which the filing date of parent application 09/646,561 has been corrected.

In accordance with 37 CFR 1.52(b)(4), Applicants have submitted a new abstract which is on separate sheet, free of any other text. Please insert the abstract into the specification following page 85 and just ahead of the SEQUENCE LISTING.

Where trademarks have been used in the specification, replacement paragraphs have been submitted in which, upon the first use of the trademark within the paragraph, the letters of the trademark have been capitalized and the trademark is followed by the generic terminology.

Claims 41-64 have been canceled and new Claims 65- 80 have been submitted. The newly submitted claims substantially track the canceled claims. However, new Claim 65 has been drafted in a means plus function format. Support for this claim can be found in the specification, for example, on page 58, lines 4-30, through page 59, lines 1-27. Accordingly, Applicants contend no new matter has been entered into the Application.

Objection to the Priority Claim

The Examiner has stated provisional application 60/078,765, to which the instant Application claims priority, fails to support the functional limitations of "capable of binding a CTLA4 or CD28 protein" or "capable of stimulating T-cell proliferation". Applicants respectfully disagree and point the Examiner to the specification of provisional application 60/078,765 (herein referred to as '765). The '765 specification, for example, page 1, lines 10-23 through page 2, lines 1-6, clearly discloses that B7 molecules are receptors for the ligands CD28 and CTLA-4. The '765 specification further discloses that such binding delivers a co-stimulatory signal to T-cells which regulates T-cell proliferation. Applicants contend it would be clear to one skilled in the art reading the specification that a functional B7 molecule will bind CD28 and/or CTLA-4 and stimulate T-cell proliferation. In view of the support cited for T-cell stimulation and CD28 and CTLA-4 binding, Applicants contend Claims 43, 45, 48, 60 and 63 are entitled to the benefit of the filing date of provisional application 60/078,765.

Absence of co-inventor Sim's signature from Declaration

Co-inventor Gek-Kee Sim has been found to be non-cooperative in parent application 09/646,561, and in other related cases, as evidenced by the previously submitted copy of Decision on Renewed Petition accepting parent application 09/646,561 without co-inventor Sim's signature As requested by the Examiner, Applicants have attached a copy of the petition under 37 CFR 1.47(a) filed with application 09/646,561. Additionally, Applicants have attached a copy of the USPTO Decision accepting the parent Application without the signature of co-inventor Gek-Kee Sim along with a copy of a letter sent from the USPTO to co-inventor Gek-Kee Sim informing her of her status as a named inventor. Finally, Applicants have attached a copy of a Declaration of Timothy McCutcheon which details attempts made by Mr. McCutcheon to reach con-inventor Sim.

Inventors

As noted by the Examiner, the Oath or Declaration listed Shumin Yang and Gek-Kee Sim as inventors, while the IDS and Application Transmittal Sheet also listed Karen S. Sellins as an inventor. Karen S. Sellins is correctly listed as an inventor on the IDS and Application Transmittal Sheet and her omission from the Oath or Declaration was an oversight. Applicants are in the process of obtaining a new Oath or Declaration signed by co-inventor Shumin Yang and co-inventor Karen S. Sellins, and will submit this Supplemental Oath or Declaration as soon as it is signed.

Information Disclosure Statement

The Examiner has stated that only three of the 43 references listed on the instant PTO-1449 have been cited in the previous Application and has invited Applicants to submit the missing references to complete the file. It is unclear to the Applicants what the Examiner is asking for. All of the relevant references that Applicants have in their possession were submitted in the parent case (09/646,561). Please clarify.

Rejections Under 35 U.S.C. §112, second paragraph - indefiniteness

The Examiner has rejected Claims 42, 43 and 52 under 35 U.S.C. §112, second paragraph as being indefinite. Specifically, the Examiner states the term "hybridizes under stringent

conditions" in Claim 42 is indefinite in that it does not specify the metes and bounds of the hybridization conditions. While the Examiner acknowledges the specification discloses parameters for calculating stringent hybridization conditions, the Examiner asserts the phrase in unclear as to which conditions are actually claimed.

While Applicants respectfully disagree with the Examiner's position, Applicants note Claims 42, 43 and 52 have been canceled. The newly submitted claim set does not contain any reference to hybridization language, rendering this rejection mute.

Rejections Under 35 U.S.C. §112, first paragraph – written description

The Examiner has rejected Claims 47 and 62 as containing subject matter not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time of filing, had possession of the claimed invention. Specifically, the Examiner states the limitation "an isolated protein of at least about 50 amino acids in length, wherein said protein comprises an at least 50 contiguous amino acid region identical in sequence to a 50 contiguous amino acid region" lack support in the specification and the claims as originally filed.

Applicants note Claims 47 and 62 have been canceled and the new claim set does not contain the above-described limitation. Therefore, this rejection is mute.

Rejections Under 35 U.S.C. §112, first paragraph – enablement

The Examiner has rejected Claims 40-45, 47-48, 51, 52, 60 and 62-63 for lack of enablement. Specifically, the Examiner states the specification enables isolated protein comprising an amino acid sequence set forth in SEQ ID NO's 7 and 17, and an isolated protein encoded by a nucleic acid sequence set forth in SEQ ID NO's 9 and 19 but fails to enable any of the remaining claimed proteins. In particular, the Examiner contends the specification fails to provide enablement for:

(a) homologues of B7-2;

(b) proteins encoded by nucleic acid molecules which hybridized under stringent conditions with a nucleic acid sequence of SEQ ID NO: 10 or 20;

(c) proteins encoded by nucleic acid molecules comprising at least 150 contiguous nucleotides from SEQ ID NO:9 or 19;

(d) proteins encoded by nucleic acid molecules at least 95% identical to SEQ ID NO: 9 or 19

(e) proteins at least about 50 amino acids in length and comprising an at least 50 amino acid region identical in sequence to SEQ ID NO:7 or 17;

(f) proteins comprising an amino acid sequence at least about 85% identical to SEQ ID NO:7 or 17; and

(g) proteins which when administered to an animal regulate a T-cell mediated immune response in said animal.

Applicants note the rejected claims have all been canceled. Additionally, the newly submitted claim set does not refer to homologues, proteins encoded by nucleic acid molecules described by their hybridization properties, proteins encoded by nucleic acid molecules of a particular length, proteins having an at least 50 amino acid region identical to a specified region in a SEQ ID NO, or proteins 85% identical to a specified SEQ ID NO.

Newly submitted Claims 69 and 75 are drawn, respectively, to proteins encoded by a nucleic acid molecule comprising a nucleic acid sequence at least about 95% identical to specified SEQ ID NO's and to proteins comprising an amino acid sequence at least about 95% identical to specified SEQ ID NO's. These claims also specify the claimed proteins have the activity of binding a CTLA4 or CD28 protein or be capable of stimulating T-cells. Applicants assert such proteins are enabled by the specification. The specification clearly discloses such proteins; see for example, page 30, lines 3-11, and page 24, lines 17-31, through page 25, lines 1-7. Based on the teaching in the specification and the state of the art of molecular biology, one skilled in the art would have no trouble envisioning and making all proteins encoded by nucleic acid molecules 95% identical to the specified SEQ ID NO or having an amino acid sequence 95% identical to the specified SEQ ID NO's. Admittedly, not all of these proteins will have the desired activity; however, the specification clearly teaches assays that can be used to test a particular protein for the desired activity; see, for example, page 59, lines 29-31, through page 60, , lines 1-27. While Applicants acknowledge the specification does not specifically disclose which amino acids can be changed while still retaining the desired activity, Applicants contend such disclosure is unnecessary. It is enough that the specification discloses several examples of the claimed proteins and also teaches methods which can be used to make or identify other proteins falling within the scope of the claims. As noted by the court in *In re Angstadt and*

Griffin (190 USPQ 214, CCPA), inventors are not required to disclose a test with every species covered by the claims since such a requirement would force inventors to carry out a prohibitive number of actual experiments. This same court held that if a disclosure were required to "provide guidance which will enable one skilled in the art to determine, *with reasonable certainty before carrying out an experiment*, whether the claimed product will be obtained, ...then all experimentation is undue since the term experimentation implies that the success of the particular activity is uncertain." Therefore, in view of the teaching of the specification and in view of the Courts opinion in Angstadt, Applicants believe the claimed proteins are enabled by the instant disclosure.

Rejections Under 35 U.S.C. §112, first paragraph – written description

The Examiner has rejected Claims 40-45, 47-48, 51, 52, 60 and 62-63 for lack of adequate written description. Specifically, the Examiner contends Applicants, at the time of filing, were not in possession of:

(a) homologues of B7-2;

(b) proteins encoded by nucleic acid molecules which hybridized under stringent conditions with a nucleic acid sequence of SEQ ID NO: 10 or 20;

(c) proteins encoded by nucleic acid molecules comprising at least 150 contiguous nucleotides from SEQ ID NO:9 or 19;

(d) proteins encoded by nucleic acid molecules at least 95% identical to SEQ ID NO: 9 or 19

(e) proteins at least about 50 amino acids in length and comprising an at least 50 amino acid region identical in sequence to SEQ ID NO:7 or 17;

(f) proteins comprising an amino acid sequence at least about 85% identical to SEQ ID NO:7 or 17; and

(g) proteins which when administered to an animal regulate a T-cell mediated immune response in said animal.

As noted above, the rejected claims have all been canceled. Additionally, the newly submitted claim set does not refer to homologues, proteins encoded by nucleic acid molecules described by their hybridization properties, proteins encoded by nucleic acid molecules of a particular length, proteins having an at least 50 amino acid region identical to a specified region in a SEQ ID NO, or proteins 85% identical to a specified SEQ ID NO.

Newly submitted Claims 69 and 75 are drawn, respectively, to proteins encoded by a nucleic acid molecule comprising a nucleic acid sequence at least about 95% identical to specified SEQ ID NO's and to proteins comprising an amino acid sequence at least about 95% identical to specified SEQ ID NO's. These claims also specify the claimed proteins have the activity of binding a CTLA4 or CD28 protein or be capable of stimulating T-cells. Applicants assert the specification provides adequate written description of such proteins. For example, the specification on page 30, lines 3-11, and page 24, lines 17-31, through page 25, lines 1-7, clearly discloses proteins encoded by a nucleic acid molecule comprising a nucleic acid sequence at least about 95% identical to specified SEQ ID NO's and to proteins comprising an amino acid sequence at least about 95% identical to specified SEQ ID NO's. While the specification does not disclose every possible sequence covered by the claims, Applicants contend such disclosure is unnecessary. The specification provides the sequence of canine B7-2. Starting from this, the limitation of "at least about 95% identical" provides a mathematical description of how far from the core B7-2 sequence one skilled in the art can stray before leaving the scope of the claims. While the specification does not explicitly list every possible variant, they are all inherently disclosed since the "95%" limitation clearly defines the boundary of the genus. One skilled in the art would have no trouble envisioning all possible sequence variations. Applicants acknowledge that the claimed proteins must also have the specified activity and that the specification does not discloses exactly which of the variant sequences would have such activity. However, Applicants have taught an activity and furthermore, have taught how to determine if a protein has such activity. Therefore, Applicants have provided a roadmap describing all proteins encompassed by the instant claims. In view of this, Applicants contend the instant invention is adequately described in the specification.

Rejection Under 35 U.S.C. §102(a)

The Examiner has rejected Claims 40, 42, 43, 47-52 and 62-64 as being anticipated by Pinelli et al. (Immunology, 1997 (Dec.), Vol. 92, No. Suppl. 1, p.39). The Examiner states Pinelli et al. (Pinelli) teach "B7 costimulatory molecules " expressed on macrophages isolated from beagle dogs. The Examiner further states that since Pinelli uses the word plural form of the word "molecule", and since the B7-1 and B7-2 molecules do not exist in a complex with each other, the canine B7-2 protein is inherent in the teaching of Pinelli.

First, Applicants note the Examiner's citation was incorrect. The article from the December 1997, Vol. 92, No. Suppl. 1, p. 39 issue of Immunology is not written by Pinelli, nor does it relate to canine B7 molecules. Instead, this article relates to a totally different subject, namely the inhibition of human T-cell proliferation using recombinant sheep LFA-3. Therefore, this article is not applicable as prior art as asserted by the Examiner. Applicants note the Examiner did provide an abstract by Pinelli, and Applicants have based their arguments on the content of this abstract.

Pinelli the levels of various co-stimulatory molecules, including B7 proteins, are decreased on the surface of macrophages following infection with *Leishmania infantum*. Applicants note Pinelli do not teach any particular sequence; they merely teach that a B7-2 protein exists on the surface of canine macrophages as detected using labeled CTLA4 protein.

Applicants note the rejected claims have all been canceled. Furthermore, proteins claimed by the newly submitted claims are all based on a very specific nucleotide and amino acid sequence discovered by the Applicants. Therefore, since Pinelli fails to provide any sequence data whatsoever, and the instant Application claims the canine B7-2 protein based on a very specific sequence, Applicants contend the instant claims cannot be anticipated by Pinelli.

The Examiner had previously stated that claims 47-50 (now canceled) and 62 –64 (now cancelled), which did refer to a particular sequence, were anticipated by Pinelli since the claimed protein was the same as that taught by Pinelli. Applicants disagree with the Examiner's position. As noted above, Pinelli did not teach any sequence at all. The presence of the canine B7-2 molecule was inferred based on the binding of a labeled B7-2 ligand, namely CTLA4. All this data demonstrated was that a CTLA4 biding protein called B7 was present on the surface of canine macrophages. The data says nothing about the sequence of this protein . More importantly, it says nothing about the relationship between the detected protein and the instantly claimed protein. The Examiner is assuming they are the same protein since they are both present in canine cells and both bind CTLA4. Without supporting evidence showing the protein of Pinelli is the same as that claimed by the Applicants, Applicants contend such supposition on the part of the Examiner is improper. In view of this, Applicants believe the newly submitted claims to be novel over Pinelli.

Rejections Under 35 U.S.C. 102(b)

The Examiner has rejected Claims 40, 42, 43, 48, 51, 52 and 63 as being anticipated by Maher et al. Specifically, the Examiner states Maher et al. (Maher) teach porcine B7-2 proteins which have greater than 80% identity with the canine B7-2 protein. Furthermore, the DNA encoding porcine B7-2 protein is greater than 80% identical to the DNA encoding canine B7-2 protein and would therefore hybridize under stringent conditions. Therefore, the claims are anticipated by Maher.

Applicants note the rejected claims have all been canceled. The newly submitted claims do not contain any hybridization language. Furthermore, the claimed variants have percent identities of at least about 95%, far above that shared with porcine B7-2 protein and DNA. In view of this, Applicants believe the newly submitted claims are not anticipated by Maher.

Rejections Under 35 U.S.C. 102(e)

The Examiner has rejected Claims 40-43 and 51-52 as being anticipated by US Patent No. 6,084,067 (the '067 patent). Specifically, the Examiner states the '067 patent teaches human B7-2 protein which has greater than 60% sequence identity with the canine B7-2 protein. Furthermore, the DNA encoding porcine B7-2 protein is greater than 77% identical to the DNA encoding canine B7-2 protein and would therefore hybridize under stringent conditions. Therefore, the claims are anticipated by the '067 patent.

Applicants note the rejected claims have all been canceled. The newly submitted claims do not contain any hybridization language. Furthermore, the claimed variants have percent identities of at least about 95% with the disclosed SEQ ID NO's, far above that shared with porcine B7-2 protein and DNA. In view of this, Applicants believe the newly submitted claims are not anticipated by the '067 patent.

Rejections Under 35 U.S.C. 103(a)

The Examiner has rejected claims 40-43, 47-52 and 62-64 as being unpatentable over Pinelli in view of US Patent 6,084,067. Specifically the Examiner states Pinelli teaches B7-2 proteins exist. Further, the '067 patent teaches isolated B7-2 proteins encoded by nucleic acids which would hybridize to those disclosed in the instant Application. The '067 patent also teaches such proteins are useful for therapeutically regulating immune responses. The Examiner

concludes it would have been obvious to one of skill in the art to apply the teachings of the '067 patent to that of Pinelli to obtain the instant invention.

Applicants note the rejected claims have all been canceled. The newly submitted claims are drawn to proteins having a basis in the disclosed SEQ ID NO's. As noted above, while Pinelli taught CTLA4-binding molecules referred to as B7 proteins existed on the surface of macrophages, Pinelli did not disclose any sequence for these proteins. Therefore, there is no indication the proteins of Pinelli are the same as those of Applicants. While one skilled in the art may have had a desire to use the canine B7-2 proteins having the instant sequences in therapeutic compositions, they could not have since the sequence was not disclosed by Pinelli. Furthermore, nothing in the '067 patent suggests, or makes obvious, the specific protein and DNA sequences claimed in the instant Application. It wasn't until the instant disclosure that such sequences were known. Therefore, since neither Pinelli nor the '067 patent provide the instantly disclosed protein and DNA sequence, neither Pinelli nor the '067 patent, alone or in comabination, can be cited as prior art against the instant application. In view of this, Applicants contend the newly submitted claims are not obvious in view of Pinelli combined with the '067 patent.

CONCLUSION

Applicants believe the current claim set to be in condition for allowance and solicit such from the Examiner. If there are any questions, the Examiner is invited to contact the undersigned at (970) 493-7272 ext. 4174.

Respectfully submitted,

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By: _____

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